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(54) Pharmaceutical compositions containing piroxicam

(57) The present invention relates to an oral pharmaceutical composition comprising piroxicam (i.e. N–(2–piridyl)–2–methyl –4–hydroxy–2H–1, 2–benzothiazine–3–carboxamide–1, 1–dioxide) as active ingredient, together with lactose as a carrier, in micronised form (i.e. at least 90% by weight of the composition having a particle size not greater than 30 μm. The composition may be made up into tablets and capsules.

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PHARMACEUTICAL COMPOSITION AND PROCESS FOR PREPARING THE SAME

The present invention relates to a homogenizate comprising piroxicam as active ingredient, to a process for preparing the same and a process for the preparation of capsule or tablet from the said homogenizate.

More particularly, the invention relates to a powder homogenizate comprising N-(2-piridyl)-2-methyl-4-hydroxy--2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (further on piroxicam) as active ingredient together with carriers, further to capsules or tablets prepared from the said homogenizate.

Piroxicam has been described first by US patent specification No. 3,591,584, the examples of which suggest the following compounds to incorporate into tablets or capsules:

tablets: piroxicam, sodium citrate, alginic acid, polyvinyl pyrrolidone, magnesium stearate;

capsules: piroxicam, calcium carbonate, polyethylene glycol.

The said patent specification does not disclose any specific data, e.g. breaking rigidity, resistance to abrasion, fluidity, disintegration time, mass density, active ingredient dissolution, being characteristic for

the tablets or the capsules.

European patent specification No. 66,459 relates to the preparation of piroxicam ethylenediamine and mono- or diethanaolamine salts having enhanced dissolving ability. The examples of this reference describe the following compositions of tablets and capsules, but the qualitative properties and dissolution curves are not taught:

Tablet:

piroxicam ethylenediamine salt	5.88 mg
corn starch USP	34.00 mg
magnesium stearate	1.04 mg

Tablets with 10, 25 and 50 mg active ingredient content can be prepared similarly, taking the proportional amounts of the ingredients.

Capsule:

piroxicam monoethanolamine salt	59.21 mg
anhydrous dicalcium phosphate	230.10 mg
corn starch	32.50 mg
sodium lauryl sulfate	0.32 mg
magnesium stearate	2.07 mg

Tablet:

piroxicam monoethanolamine salt	23.92 mg
microcrystalline cellulose	311.03 mg
modified, pregelatinized starch	84.00 mg
magnesium stearate	0.945 mg
sodium lauryl sulfate	0.105 mg

Tablet:

piroxicam monoethanolamine salt	23.69 mg
anhydrous dicalcium phosphate	113.37 mg
polyvinyl pyrrolidone	50.00 mg
modified, pregelatinized starch	10.0 mg
magnesium stearate	2.65 mg
sodium lauryl sulfate	0.294 mg

When a pharmaceutical composition comprising piroxicam as active ingredient is prepared, the following problems arise:

a) Piroxicam is poorly soluble in aqueous medium, therefore in order to eliminate this disadvantage European patent specification No. 66,459 suggests the use of a salt of piroxicam.

b) In the course of a wet granulation process the composition gets coloured due to the effect of the aqueous or hydroxyl-group-containing granulating liquid, thus the composition does not meet the international standard.

c) The adsorption of the active ingredient from the pharmaceutical formulation is a very important characteristic which can be measured by expensive biological tests; thus

it is preferred if the different dosage forms have the same composition.

d) When the composition is formulated by wet granulation technique, the homogeneous distribution of the ingredients is assured, while when dry homogenization is applied, in case of non-properly selected excipients, especially in the course of tabletting, sorting owing to the gravitational filling uneven distribution of the active agent may occur which may result in non-admitted scattering of the active ingredient.

The aim of the invention was to prepare a homogenizate

1) which is suitable for preparing tablets and capsules of the same composition,
2) in which, independently from the crystal form of the active ingredient, the dissolution values and qualitative parameters of the capsule and tablet are suitable,
3) in which the scattering of the active ingredient content is in accordance with the standards,
4) which can be in dry medium.

No composition meeting the above requirements can be found in the prior art.

In the course of our experiments it was found that with the composition comprising piroxicam as active ingredient according to USP XXI the desired <u>in vitro</u> dissolution level could not be achieved. This dissolution rate would be obtained if at least 75% by mass of the active ingredient content were dissolved out from the composition within 45 minutes.

According to our measurements, from the standard composition comprising piroxicam as active ingredient 42 to 45% by mass of the active ingredient content were dissolved out within 45 minutes at a temperature of 37 °C, at a stirring rate of 50 revolution/minute, by using artificial gastric juice under the prescriptions of USP XXI in a rotating dissolving equipment.

The scattering of the active ingredient content in pharmaceutical formulations comprising piroxicam as active ingredient may be RSD = 6.0% according to USP XXI.

Now it has been found that if piroxicam crystals are micronized below a particle size of 30 /um, preferably below 10 /um, and if possibly mannitol and silica are added, the composition comprising the micronized piroxicam crystals assures the desired dissolution values and these values can safely be maintained.

Based on the above, the homogenizate according to the invention is composed of

1 part by weight of N-(2-piridyl)-2-methyl-4-hydroxy-2H--1,2-benzothiazine-3-carboxamide-1,1-dioxide as active ingredient which at least in 90% by mass has a particle size of at most 30 /um, preferably 10 /um,

if desired, 0.1 to 5.0 parts by mass, preferably 1 part by mass, of mannitol optionally of the same particle size,

if desired, 0.005 to 0.15 parts by mass, preferably 0.06 to 0.1 parts by mass of silica optionally of the same particle size,

5 to 25 parts by mass, preferably 8 to 18 parts by mass, of spray-dried lactose which at least in 80% by mass has a particle size of 80 to 200 /um,

if desired, 0.5 to 6.0 parts by mass, preferably 1.5 to 4.0 parts by mass, of a disintegrant, preferably corn starch,

if desired, 0.005 to 0.05 parts by mass, preferably 0.01 to 0.02 parts by mass, of a surface active agent, preferably sodium lauryl sulfate, and

if desired, 0.05 to 0.5 parts by mass, preferably 0.1 to 0.2 parts by mass, of a lubricant, preferably magnesium stearate.

The lactose has preferably a surface pore size of 10 to 20 /um.

The homogenizate according to the invention is prepared by

micronizing 1 part by mass of N-(2-piridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide as active ingredient with or without 0.1 to 5.0 parts by mass, preferably 1 part by mass of mannitol and 0.005 to 0.15 parts by mass, preferably 0.06 to 0.1 parts by mass, of silica in such a manner that at least 90% by mass of the mixture have a particle size of at most 30 /um, preferably at most 10 /um, or if mannitol and silica have not been micronized together with the active ingredient, if desired, adding mannitol and/or silica in the above amounts to the mixture after micronization,

then homogenizing the mixture thus obtained with

the partial or complete mixture of 5 to 25 parts by mass, preferably 8 to 18 parts by mass of spray-dried lactose which at least in 80% by mass has a particle size of 80 to 200 /um, a disintegrant such as corn starch in an amount of 0.5 to 6.0 parts by mass, preferably 1.5 to 4.0 parts by mass, a surface active agent such as sodium lauryl sulfate in an amount of 0.005 to 0.05 parts by mass, preferably 0.01 to 0.02 parts by mass, a lubricant such as magnesium stearate in an amount of 0.05 to 0.5 parts by mass, preferably 0.1 to 0.2 parts by mass, and

if desired, filling the thus-obtained homogenizate into capsules or pressing it into tablets.

The composition according to the invention has anti-rheumatic and antiinflammatory activity.

The piroxicam capsules according to the invention show the following dissolution data:

Dissolution of the active ingredient

5 minutes	15 minutes	45 minutes
69%	86%	92%

The suitably low scattering of the active ingredient content of the tablet or capsule and the high and safe dilution of the homogenizate could be achieved by mixing the piroxicam with spray-dried lactose of a surface pore size of 10 to 20 /um which at least in 80% by weight has a particle size of 80 to 200 /um. Thus a so-called 'arranged' mixture could be achieved, in which the micronized piroxicam

particles are adhered into the pores of the lactose, while the preferable flowing characteristics of lactose are maintained, enabling the easy preparation of the homogenizate and the easy formulation of tablets or capsules from the homogenizate.

The scattering of the active ingredient content in the capsules is about RSD = 2.0%, while in the tablets is about RSD = 2.5%.

The invention is further illustrated by the following, non-limiting examples.

Example 1

Micronizing

The particle size distribution of piroxicam of a quality according to USP XXI measured by microscope:

maximal size:	500 /um
above 100 /um:	15 %
below 100 /um:	85 %
below 50 /um:	50 %
below 20 /um:	30 %
below 10 /um:	10 %
below 5 /um:	5 %.

The micronizing is carried out in a Fryma JM-80 air-jet mill.

300 g of piroxicam, 300 g of mannitol and 18 g of aerosil 200 (SiO_2) are charged into the mixer and the components are mixed. The powdering is carried out by adjusting the charger and the air valve to 6 bar.

The particle size of the micronized powder mixture is as follows:

90% by weight under 10 /um,

10% by weight between 10 and 30 /um.

The bulk density of the micronized powder mixture is as follows:

loose 3.12 ml/g

compacted 2.81 ml/g.

Example 2

Trituration

1800 g of lactose (DCL 11) and 3.6 g of sodium lauryl sulfate are homogenized according to the rules of triturate preparation. A bronze sieve cloth of 250 µm mesh size is used in the course of the process. The triturate is prepared in 40 minutes.

Example 3

Homogenization

The homogenization is carried out in a homogenizator of Lödige FM-50 type. 3582 g of lactose (DCL 11) and 1160.4 g of corn starch are charged into the equipment and the micronizate and triturate prepared according to Examples 1 and 2 are added. The equipment is closed and the powder mixture is homogenized for 19 minutes by moving the plough arms. Then 0.3 g of magnesium stearate is added and the mixture is further homogenized for 1 minute. The complete homogenization time is one hour.

The bulk density of the homogenized powder mixture is as follows:

loose 1.56 ml/g

compacted 1.20 ml/g

Mass density: 0.72 g/ml.

Flowability: 2.85 ml/sec.

The sieve analysis of the homogenized powder mixture is as follows:

between 0.32 to 0.20 mm: 6 to 15%,

between 0.20 to 0.10 mm: 35 to 45%,

below 0.10 mm: 45 to 55%.

Example 4

Capsulation and tabletting

Preparation of capsules and tablets of 10 mg

From the homogenizate according to Example 3 capsules and tablets of 10 mg are prepared with the following composition:

	Capsule	Tablet
piroxicam USP XXI	10.00 mg	10.00 mg
mannitol	10.00 mg	10.00 mg
aerosil 200 (colloidal SiO_2)	0.60 mg	0.60 mg
sodium lauryl sulfate	0.12 mg	0.12 mg
lactose (DCL 11)	179.40 mg	179.40 mg
corn starch	38.68 mg	38.68 mg
magnesium stearate	1.20 mg	1.20 mg
	240.00 mg	240.00 mg

The capsulation is carried out in a capsule filling machine of Zanasi LZ-64 type.

Mass of the capsule filling: 240 mg

Type and size of the capsule: Capsugel Coni-snap, 2-s Maroon op/Buff op, 33/35 or White L 500-Pink L 770

The homogenizate according to Example 3 is directly tabletted. The tabletting is carried out on a tabletting machine of Erweka E XI by using a flat, flanged pressing tool of 9 mm.

The characteristic properties of the capsules are as follows:

Disintegration time: 3 minutes

Dissolution of the active ingredient from the capsule:

5 minutes	15 minutes	45 minutes
69%	86%	92%

Scattering of the active ingredient: RSD = 1.8%.

The characteristic properties of the tablets are as follows:

Tabletting	Pressing power		
	10 kN	15 kN	20 kN
breaking resistance	43.2 N	67.7 N	86.5 N
abrasion loss at a rate of 4 minutes/100 revolution	0.43 %	0.44 %	0.74 %
disintegration time	1.6 min.	1.5 min.	2.6 min.

Dissolution of the active ingredient from the tablet prepared with 20 kN pressing power:

15 minutes	30 minutes	45 minutes
83%	87.5%	88.5%

Scattering of the active ingredient: RSD = 2.5 %.

Preparation of capsules and tablets of 20 mg

Tablets and capsules containing 20 mg of piroxicam are similarly prepared. The composition of the tablets and capsules is as follows:

	Capsule	Tablet
piroxicam USP XXI	20.00 mg	20.00 mg
mannitol	20.00 mg	20.00 mg
aerosil 200 (colloidal SiO_2)	1.20 mg	1.20 mg
sodium lauryl sulfate	0.24 mg	0.24 mg
lactose (DCL 11)	162.00 mg	162.00 mg
corn starch	36.36 mg	36.36 mg
magnesium stearate	1.20 mg	1.20 mg
	240.00 mg	240.00 mg

The characteristics of the capsule are as follows:
Active ingredient dissolution: 100% within 45 minutes.
Scattering of the active ingredient: RSD = 2.1 %.

The characteristics of the tablet are as follows:
Active ingredient dissolution: 100% within 10 minutes.
Scattering of the active ingredient: RSD = 2.5 %.

Example 5

Preparation of capsules and tablets of 10 mg or 20 mg mass

The process of Examples 1 to 4 is followed except that the micronizing of piroxicam according to Example 1 is carried out without mannitol or without mannitol and silica.

The composition of capsules and tablets of 10 mg without mannitol and silica is as follows:

	Capsule	Tablet
piroxicam USP XXI	10.00 mg	10.00 mg
sodium lauryl sulfate	0.12 mg	0.12 mg
lactose (DCL 11)	190.00 mg	190.00 mg
corn starch	38.68 mg	38.68 mg
magnesium stearate	1.20 mg	1.20 mg
	240.00 mg	240.00 mg

The composition of capsules and tablets of 20 mg without mannitol is as follows:

	Capsule	Tablet
piroxicam USP XXI	20.00 mg	20.00 mg
aerosil 200 (colloidal SiO_2)	1.20 mg	1.20 mg
sodium lauryl sulfate	0.24 mg	0.24 mg
lactose (DCL 11)	162.00 mg	162.00 mg
corn starch	36.36 mg	36.36 mg
magnesium stearate	1.20 mg	1.20 mg
	220.00 mg	220.00 mg

CLAIMS

1. Pharmaceutical composition comprising N-(2-piridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide as active ingredient, which comprises

1 part by weight of N-(2-piridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide as active ingredient which at least in 90% by mass has a particle size of at most 30 µm, preferably 10 µm,

if desired, 0 to 5.0, e.g. 0.1 to 5.0, parts by mass, preferably 1 part by mass, of mannitol optionally of the same particle size,

if desired, 0 to 0.15, e.g. 0.005 to 0.15, parts by mass, preferably 0.06 to 0.1 parts by mass, of silica optionally of the same particle size,

5 to 25 parts by mass, preferably 8 to 18 parts by mass, of spray-dried lactose which at least in 80% by mass has a particle size of 80 to 200 µm,

if desired, 0 to 6.0, e.g. 0.5 to 6.0, parts by mass, preferably 1.5 to 4.0 parts by mass, of a disintegrant, preferably corn starch,

if desired, 0 to 0.05, e.g. 0.005 to 0.05, parts by mass, preferably 0.01 to 0.02 parts by mass, of a surface active agent, preferably sodium lauryl sulfate, and

if desired, 0 to 0.5, e.g. 0.05 to 0.5, parts by mass, preferably 0.1 to 0.2 parts by mass, of a lubricant, preferably magnesium stearate.

2. Process for the preparation of a pharmaceutical composition comprising N-(2-piridyl)-2-methyl-4-hydroxy--2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide as active ingredient, which comprises

micronizing 1 part by mass of N-(2-piridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide as active ingredient with or without 0.1 to 5.0 parts by mass, preferably 1 part by mass of mannitol and 0.005 to 0.15 parts by mass, preferably 0.06 to 0.1 parts by mass, of silica in such a manner that at least 90% by mass of the mixture have a particle size of at most 30 /um, preferably at most 10 /um, or if mannitol and silica have not been micronized together with the active ingredient, if desired, adding mannitol and/or silica in the above amounts to the mixture after micronization,

then homogenizing the mixture thus obtained with the partial or complete mixture of 5 to 25 parts by mass, preferably 8 to 18 parts by mass, of spray-dried lactose which at least in 80% by mass has a particle size of 80 to 200 /um, a disintegrant such as corn starch in an amount of 0.5 to 6.0 parts by mass, preferably 1.5 to 4.0 parts by mass, a surface active agent such as sodium lauryl sulfate in an amount of 0.005 to 0.05 parts by mass, preferably 0.01 to 0.02 parts by mass, a lubricant such as magnesium stearate in an amount of 0.05 to 0.5 parts by mass, preferably 0.1 to 0.2 parts by mass and

if desired, filling the thus-obtained homogenizate into capsules or pressing it into tablets.

3. The composition substantially as hereinbefore described in Examples 1 to 3, in Example 4 or in Example 5.

5. The composition as claimed in claim 1 or in claim 3 in unit dosage form, e.g. tablets or capsules.

5. A process of making the composition as claimed in claim 1, substantially as hereinbefore described in Examples 1 to 3 or in Example 4 or in Example 5.

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